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Formulations of Ramipril

FIELD OF THE INVENTION

The present invention relates to a stable pharmaceutical formulation of ramipril.

TECHNICAL BACKGROUND AND PRIOR ART

Ramipril, (2*S*,3*aS*,6*aS*)-1[(*S*)-*N*-[(*S*)-1-carboxy-3-phenylpropyl] alanyl] octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid, 1-ethyl ester is an angiotensin converting enzyme (ACE) inhibitor. Ramipril is used for the treatment of hypertension, heart failure, stroke, myocardial infarction, diabetes and cardiovascular disease.

Ramipril and the acid form, ramiprilat, is described in EP 0 097 022 B1.

The preparation of stable pharmaceutical formulations of ramipril is complicated since it is susceptible to certain types of degradation. Ramipril can undergo cyclization via internal nucleophilic attack to form substituted diketopiperazines and also degrade via hydrolysis and oxidation.

EP 0 280 999 B1 describes a composition comprising ACE inhibitor (i.e. ramipril), an alkali or alkaline earth metal carbonate and saccharide wherein the ACE inhibitor is stabilized against degradation (cyclization, discoloration and hydrolysis) by means of the other mentioned ingredients. In the specifications the relevant saccharides are lactose and mannitol. Modified starch is mentioned as disintegrant in the specification.

EP 0 317 878 B1 claims a stable, compressed pharmaceutical formulation containing a compound of a defined formula (i.e. ramipril) wherein, for stabilization before compression, a compound of the formula is a) coated with a polymeric, physiologically tolerated protective coating, or b) mixed with a physiologically tolerated buffer which ensures that a pH in the weakly acidic to

weakly alkaline range is set up in a pharmaceutical formulation in the presence of moisture, where sodium bicarbonate is excepted as buffer, or c) mixed with a physilogically tolerated buffer which ensures that a pH in the weakly acid to weakly alkaline range is set up in a pharmaceutical formulation in the presence of moisture, and is coated with a polymeric, physiologically tolerated protective coating, where, in the case of stabilization according to b) with alkali metal or alkaline earth metal carbonate, the formulation is free of sugar.

SUMMARY OF THE INVENTION

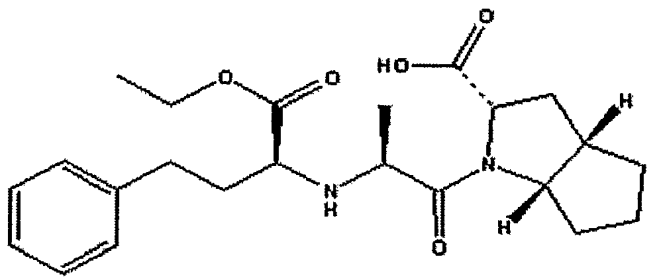
In an attempt to prepare a stable tablet formulation of ramipril, it was discovered that useful formulations can be produced by the use of calcium sulphate dihydrate (e.g. Compactrol) as filler material.

Properties of calcium sulphate are described in A. H. Kibbe, Handbook of pharmaceutical excipients, 73 – 76, American Pharmaceutical Association, Washington, and Pharmaceutical Press, London, 2000.

Calcium sulphate dihydrate is known as an inert diluent in compressed tablets. However, it was surprising that the stability of the tablets proved to be very satisfying.

DETAILED DESCRIPTION

The invention provides a pharmaceutical formulation comprising ramipril,



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Compactrol as filling agent, and sodium hydrogen carbonate as stabilation agent.

The pharmaceutical formulation of the present invention comprises typically:

a) 0.1 – 5.0% w/w of ramipril;

b) 50 - 95% w/w of Compactrol;

c) 0.1 – 5.0% w/w of sodium hydrogen carbonate;

and optionally disintegrant (e.g. starch), binder and/or lubricant (e.g. sodium stearyl fumarate).

The formulation optionally also includes hydrochlorothiazide (HCT).

For the tablet formulation containing 1.25 mg ramipril, the preferred amount of ramipril is 0.5-1.5% w/w, the amount of Compactrol is 85-90% w/w, the amount of sodium hydrogen carbonate is 0.5-1.5% w/w, the amount of starch pregelatinised is 7-13% w/w and the amount of sodium stearyl fumarate is 0.5-1.5% w/w.

For the tablet formulation containing 2.5 mg, 5 mg and 10 mg ramipril, the preferred amount of ramipril is 1.4-2.5% w/w, the amount of Compactrol is 78-95% w/w, the amount of sodium hydrogen carbonate is 1.4-2.5% w/w, the amount of starch pregelatinised is 7-13% w/w and the amount of sodium stearyl fumarate is 0.5-1.5% w/w.

For the tablet formulation containing 2.5 mg ramipril/2.5 mg hydrochlorothiazide and 5 mg ramipril/25 mg hydrochlorothiazide, preferred amount of ramipril is 1.4-2.5% w/w, the amount of hydrochlorothiazide is 8.5-10.5% w/w, the amount of Compactrol is 65-75% w/w, the amount of sodium hydrogen carbonate is 1.0-2.5% w/w, the amount of starch pregelatinised is 12-18% w/w and the amount of sodium stearyl fumarate is 0.5-1.5% w/w.

Since ramipril is susceptible to certain types of degradation, there are several impurities formed during the manufacturing process and storing of the tablet. It

is of high importance to minimize this degradation. The strength of different exipients was adjusted until a useful formulation was found.

There are certain criterias that these componds are not allowed to exceed. The present formulation has proved to be stable.

Ramipril diketopiperazine is one of the compounds formed via degradation. The present formulation proved to be especially stable with regard to formation of the diketopiperazine.

EXAMPLES

The following example is merely illustrative of the present invention and it should not be considered as limiting the scope of the invention.

Example 1

Formulation for 1.25 mg ramipril tablets

Ramipril	0.96%
Compactrol	87.08 % w/w
Sodium hydrogen carbonate	0.96% w/w
Starch pregelatinised	10.00% w/w
Sodium stearyl fumarate	1.00% w/w

Example 2

Formulation for 2.5 mg, 5 mg and 10 mg ramipril tablets

Ramipril	1.9% w/w
Compactrol	85.2 % w/w
Sodium hydrogen carbonate	1.9% w/w
Starch pregelatinised	10.0% w/w
Sodium stearyl fumarate	1.0% w/w

Example 3

Formulation for 2.5/12.5 mg and 5/25 mg ramipril hydrochlorothiazide (HCT) tablets

Ramipril	1.9% w/w
Hydrochlorothiazide	9.6% w/w
Compactrol	70.5 % w/w
Sodium hydrogen carbonate	1.9% w/w
Starch pregelatinised	15.0% w/w
Sodium stearyl fumarate	1.0% w/w

Example 4

Stability of 5 mg and 10 mg tablets prepared in Example 2 and of marketed preparation were tested at 40°C and 75% relative humidity (RH) for six months. Conversion of ramipril into ramipril diketopiperazine was assayed and measured as relativeomount of initial amount of ramipril.

5 mg

	Assay	Ramipril diketopiperazine
Tablets from Ex. 2	4.0%	0.478-1.06%
Marketed prepn**.	4.0%	2.77%

10 mg

	Assay	Ramipril diketopiperazine
Tablets from Ex. 2	4.0%	0.471-0.806%
Marketed prepn**.	4.0%	2.27%

**Ramitab™ ramipril 5 and 10 mg tablets

The example demonstates a very good stability with regard to ramipril diketopiperazine formation.

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CLAIMS

1. A tablet formulation comprising:

a) 0.5 – 5% w/w of ramipril;

b) 50 - 95% w/w of calcium sulphate dihydrate; and

c) 0.1 – 5% w/w of sodium hydrogen carbonate,

optionally in combination with a disintegrant, binder and lubricant and other excipients.

2. The tablet formulation of claim 1, wherein the calcium sulphate dihydrate is Compactrol.

3. The tablet formulation of claim 1 or claim 2, additionally in combination with a diuretic.

4. The tablet formulation of claim 3, wherein the diuretic is hydrochlorothiazide.

5. The tablet formulation of any of claims 1 to 4, wherein the disintegrant and binder is pregelatinised starch.

6. The tablet formulation of any of claims 1 to 5, wherein the lubricant is sodium stearyl fumarate.

7. The tablet formulation of claim 1 or claim 2 containing 1.25 mg ramipril, wherein the amount of ramipril is 0.5-1.5% w/w, the amount of Compactrol is 85-90% w/w, the amount of sodium hydrogen carbonate is 0.5-1.5% w/w, the amount of starch pregelatinised is 7-13% w/w and the amount of sodium stearyl fumarate is 0.5-1.5% w/w.

8. The tablet formulation of claim 1 or claim 2 containing 2.5 mg, 5 mg or 10 mg ramipril, wherein the amount of ramipril is 1.4-2.5% w/w, the amount of Compactrol is 78-95% w/w, the amount of sodium hydrogen carbonate is 1.4-

2.5% w/w, the amount of starch pregelatinised is 7-13% w/w and the amount of sodium stearyl fumarate is 0.5-1.5% w/w.

9. The tablet formulation of any of claims 1 to 4, containing 2.5 mg ramipril/2.5 mg hydrochlorothiazide or 5 mg ramipril/25 mg hydrochlorothiazide, wherein the amount of ramipril is 1.4-2.5% w/w, the amount of hydrochlorothiazide is 8.5-10.5% w/w, the amount of Compactrol is 65-75% w/w, the amount of sodium hydrogen carbonate is 1.0-2.5% w/w, the amount of starch pregelatinised is 12-18% w/w and the amount of sodium stearyl fumarate is 0.5-1.5% w/w.

ABSTRACT

The present invention relates to stable tablet formulations of ramipril.